UPPER EXTREMITY MUSCULOSKELETAL MANIFESTATIONS OF DIALYSIS-ASSOCIATED AMYLOIDOSIS

Daniel C. Fitzpatrick, M.S., Medical Student
Peter J. L. Jebson, M.D., Fellow Associate
Steven M. Madey, M.D., Resident
Curtis M. Steyers, M.D., Professor

"Dialysis-associated amyloidosis" is a recently identified complication of uremic patients undergoing long-term hemodialysis[1-6]. The inability of both cuprophane dialysis membranes to filter, and renal failure patients to catabolize the plasma protein β-2 microglobulin, results in the accumulation and subsequent conversion of this substance to amyloid fibrils. Amyloid is deposited predominantly in the musculoskeletal system in synovial, articular and periarticular tissue, resulting in a variety of conditions. The precise mechanism of β-2 microglobulin conversion to amyloid and the reason for the preferential accumulation of amyloid in the musculoskeletal system is unknown. The prevalence of these associated musculoskeletal conditions is directly proportional to the duration of dialysis. Thus, with the increasing length of survival of hemodialysis patients, those involved in their orthopaedic care will begin encountering this unusual, yet distinct, form of secondary amyloidosis. The purpose of this paper is to review the clinical, roentgenographic and pathologic features of dialysis-associated amyloidosis as seen in the upper extremity.

CARPAL TUNNEL SYNDROME

Many reports document a high incidence of hand pain and numbness in chronic renal failure patients on long term hemodialysis[7-15]. The proposed mechanisms for these symptoms include carpal tunnel syndrome (CTS) caused by edema of the flexor retinaculum, venous pooling associated with superficial vein valvular destruction distal to the fistula, and amyloid deposition in the transverse retinacular ligament. Hand numbness can also result from median nerve ischemia caused by radial steal syndrome or occur as part of the generalized peripheral neuropathy that is commonly seen in this patient population[16,17]. Although all of the above mechanisms are accepted and may occur independently or in association with one another, compression of the median nerve by amyloid in the transverse retinacular ligament (TCL), specifically by β-2 microglobulin deposits, is the most consistent finding and the most thoroughly investigated phenomena. Indeed, β-2 microglobulin is deposited in other tissues surrounding the median nerve, including tenosynovium and within the flexor tendons, but has not been found in the nerve itself or in the epineurium[18,19].

The incidence of dialysis associated carpal tunnel syndrome is directly related to the duration of dialysis therapy. The reported rates for patients who have undergone dialysis for less than 14 years of therapy are between 12% and 37%[14]. After 14 to 20 years of dialysis the incidence increases to 60%. Finally, in those patients surviving 25 years of dialysis, all have evidence of carpal tunnel syndrome[11,19].

Diagnostic evaluation includes neurophysiologic testing to assess median nerve conduction velocity across the wrist. Neurophysiologic testing is particularly helpful in differentiating the symptoms of carpal tunnel syndrome from other causes of pain and paraesthesias such as radial steal syndrome, which causes a painful ischemia of the digits deprived of shunted blood, or the generalized metabolic polyneuropathy that is seen in uremic patients[15].

The natural history of CTS in chronic dialysis patients is not known but the majority of studies indicate that compression of the median nerve is progressive. An exception is noted in those patients with dialysis associated CTS who undergo renal transplantation. Renal transplantation has been reported to improve CTS symptoms in isolated cases. The results of conservative treatment of CTS secondary to amyloidosis are also not well defined. Most studies suggest that surgical treatment is inevitable in the hemodialysis patient with CTS. Encouraging results have been reported by various authors. Those patients with a shorter duration of symptoms (defined as less than 2 years) appear to have a better outcome after surgery[15,20,21].

ARTHRALGIAS AND DESTRUCTIVE ARTHROPATHY

Destructive arthropathy is a common feature of dialysis associated amyloidosis[10,23,24]. This arthropathy appears to

Division of Hand and Microsurgery, Department of Orthopaedics Surgery, University of Iowa Hospitals & Clinics, Iowa City, Iowa 52242

Correspondent:
Peter J.L. Jebson, MD
Dept. of Orthopaedic Surgery
University of Iowa Hospitals & Clinics
Iowa City, IA 52242
(319) 356-3637

be related to β-2 microglobulin deposition in both the bone and surrounding soft tissues of the joint[23]. Congo red staining and immunohistology have documented amyloid β2-microglobulin deposition in synovial fluid and joint lining[18].

Amyloid has not been detected in destructive arthropathies involving the small joints of the hand[24]. However, the precise role of β-2 microglobulin in the pathogenesis of a destructive arthropathy is unknown. Joint involvement is usually symmetric and most frequently involves in the glenohumeral joint. Shoulder pain is the presenting symptom in 25%-50% of patients and is eventually present in up to 80% of patients. Other joints, including the thoracic and lumbar spine, knee, wrist, and small joints of the hands may also be involved[10,23,24]. Patients typically present with joint pain, swelling and loss of motion. Like many of the other musculoskeletal manifestations of hemodialysis associated amyloidosis, the prevalence of these various joint arthropathies appears to increase with the duration of dialysis, and has been reported to occur in up to 80% of patients who have been on dialysis for more than 10 years. Interestingly, renal transplantation has been shown to reduce the incidence of arthralgias. However, transplantation does not seem to reverse existing bony changes or prevent further joint deterioration once the initial cartilage destruction has occurred.

BONE CYSTS

Direct amyloid invasion with replacement of subchondral bone results in the formation of cysts that are often referred to as "intraosseous amyloidomas"[25]. These bone cysts are usually juxta-articular and appear as multiple lytic, well defined lesions that are invariably surrounded by a thin sclerotic margin. Cortical destruction and extension of the cyst to the articular surface can occur. The most common upper extremity "amyloidoma" locations include the distal clavicle, anatomical neck of the humerus, and carpus[15,24-27]. However, amyloid bone cysts have also been reported in the cervical spine, glenoid, radius, ulna, metacarpals and phalanges[15,24-27]. Carpal cysts tend to localize to the radial side and most commonly involve the scaphoid and lunate (Figure 1).

Amyloid bone cysts may be asymptomatic in up to half of involved patients. The cysts first appear between five and fifteen years after the commencement of hemodialysis and after ten years of dialysis, it has been estimated that 50-60% of all hemodialysis patients will have evidence of amyloid bone cyst formation. Pathologic fracture through amyloidomas have been reported in both the upper and lower extremities[27]. Most fractures heal uneventfully with standard treatment methods, however, nonunion can occur but seems to be unique to pathologic femoral neck fractures[27].

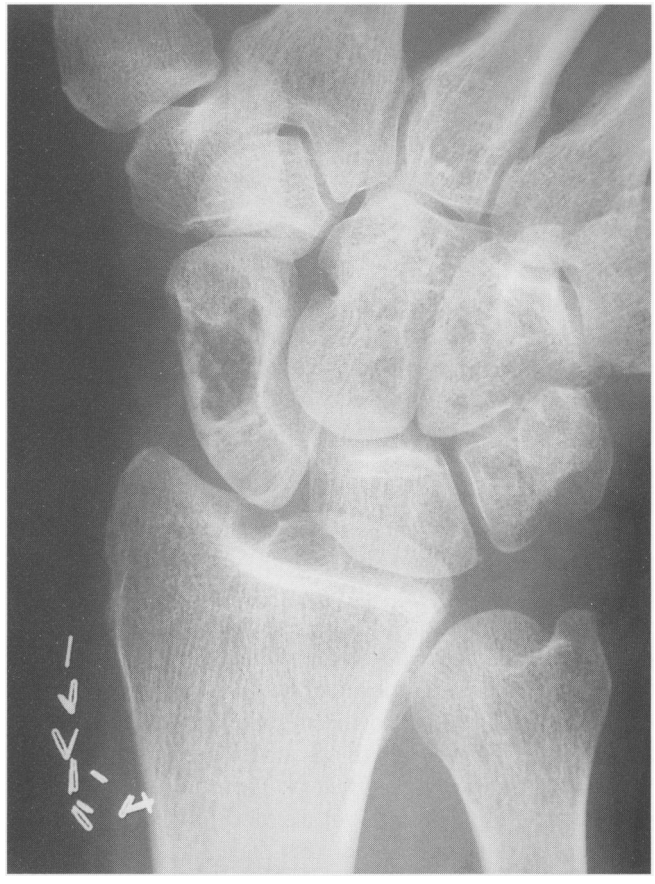

Figure 1. AP view of the hand demonstrating classic amyloid cysts throughout the carpus and distal radius. Note the large cyst in the scaphoid, a typical location and appearance.

The management of asymptomatic amyloid bone cysts is serial observation. Painful lesions may require curettage and bone grafting. The majority of cysts enlarge over time and an annual skeletal survey involving posteroanterior views of both hands and wrists and anteroposterior views of both shoulders and the pelvis has been recommended to avoid the morbidity of pathologic fracture[24,27] (Figures 2 and 3). The diagnosis of amyloid bone cyst formation is usually presumptive in the hemodialysis patient with the aforementioned characteristic radiographic features. However, definitive diagnosis may be required in atypical lesions and is usually performed via a computerized tomography guided biopsy. Congo red staining should be performed to identify amyloid deposition. Such specialized staining helps distinguish amyloidomas from brown tumors of secondary hyperparathyroidism, multiple myeloma, and metastatic disease which can also occur in the hemodialysis patient.

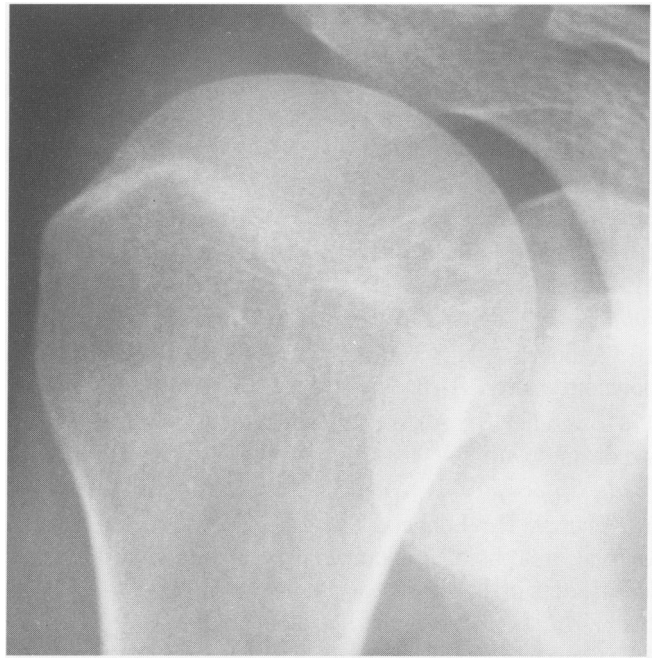

Figure 2. AP view of the shoulder illustrating biopsy proven amyloid cysts in the humeral head.

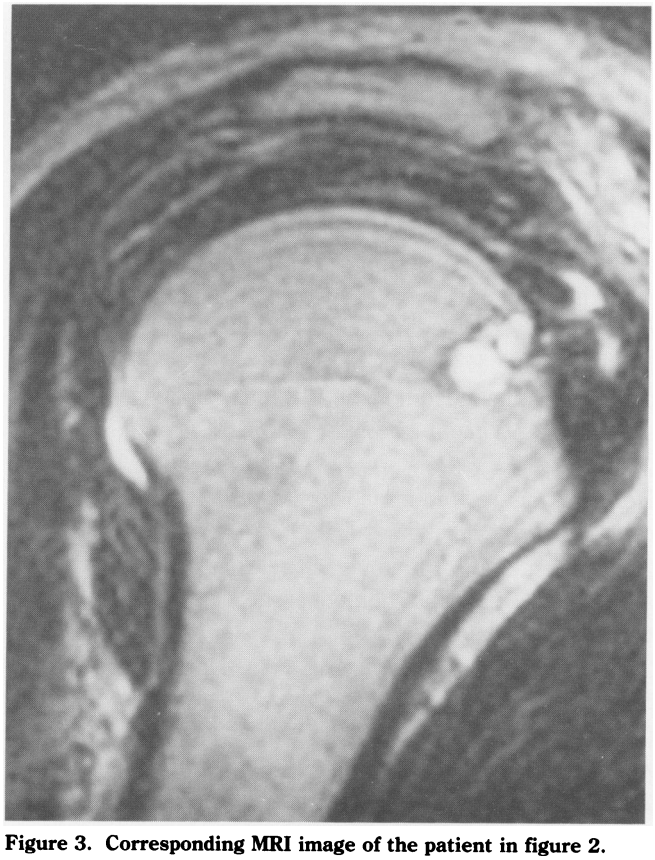

Figure 3. Corresponding MRI image of the patient in figure 2.

TENDON RUPTURE

Spontaneous tendon rupture is uncommon in dialysis associated amyloidosis, but has been reported by several authors. The largest series was reported by Kurer et al., who evaluated 83 renal failure patients who had undergone dialysis for more than 10 years. Six patients had various tendon ruptures; two involved the upper extremity with a digital flexor tendon and extensor tendon rupture. In both cases, the ruptured tendons were repaired primarily with good results. Interestingly, amyloid infiltration was identified at the site of rupture in both patients[15].

FLEXOR TENOSYNOVITIS AND JOINT CONTRACTURES

Flexor tenosynovitis is a common finding in dialysis associated amyloidosis patients. β-2 microglobulin is deposited in both flexor tenosynovium and the soft tissues of the palm. This palmar deposition results in a subcutaneous mass which produces displacement and prominence of the digital flexor tendons during range of motion. This has been referred to as the "guitar string sign" and supposedly, if seen in a renal failure patient on dialysis who has shoulder pain, is considered pathognomonic of β-2 amyloidosis[24].

Bardin evaluated 18 patients on chronic hemodialysis who had biopsy proven β-2 amyloidosis involving various components of the musculoskeletal system[3]. Four patients had tenosynovitis of the digital flexor tendons. Typical findings included palmar swelling, digital pain and limited extension of the involved digits. Ogawa performed Congo red staining on tissue obtained from 45 hemodialysis patients who had undergone a carpal tunnel release and flexor tenosynovectomy[28]. Approximately 80% of the tissue samples were positive, revealing the presence of amyloid fibrils.

Kurer identified four patients with flexor tendon contractures and finger stiffness from a series of 83 patients who had been dialyzed for a minimum of 15 years[15]. On surgical exploration, gross amyloid infiltration within the tenosynovium was found. The infiltration was so extensive that complete excision was often not feasible. Despite the significant improvement in hand function occurring in the majority of patients following partial amyloid excision, residual weakness and joint contractures were common[15].

Flipo identified two patients with destructive arthropathies of the metacarpophalangeal and interphalangeal joints who had associated flexor tenosynovitis[23]. The presence of both a destructive arthropathy and tenosynovitis was significantly debilitating and resulted in persistent pain and swelling and an inability to fully extend the involved digit.

TRIGGER FINGER

Digital triggering occurs secondary to amyloid tenosynovitis. Standard nonoperative treatment includes steroid

injection into the flexor tendon sheath and splinting. Recalcitrant cases often require surgical release of the A1 pulley of the flexor sheath combined with a tenosynovectomy. In chronic hemodialysis patients with carpal tunnel syndrome, triggering of the digits appears to occur at a significantly higher rate than in non-dialysis patients.

REFERENCES

1. Cary, N.R.B.; Sethi, D.; Brown. E.A.; et al.: Dialysis arthropathy: amyloid or iron? *British Medical Journal,* 293:392, 1986.
2. Bardin, T.; Zingraff, J.; Shirahama, T.; et al.: Hemodialysis-associated amyloidosis and β-2 microglobulin. *Am. J. Med.,* 83:419, 1987.
3. Bardin, T.; Kuntz, D.; Zingraff. J.; et al.: Synovial amyloidosis in patients undergoing long-term hemodialysis. *Arthritis Rheum.,* 28:1052, 1985.
4. Gejyo, F.; Yamada, T.; Odani, S.; et al.: A new type of amyloid protein associated with hemodialysis was identified as beta-2 microglobulin. *Biochem. Biophys Res. Commun.,* 129:701, 1985.
5. Morita, T.; Suzuki, M.; Kamimusa, A.; Hirasawa, Y.: Amyloidosis of a possible new type in patients receiving long-term hemodialysis. *Arch Pathol. Lab. Med.,* 109:1029, 1985.
6. Shirahama, T.; Skinner, M.; Cohen, A.S.; et al.: Histochemical and immunohistochemical characterization of amyloid associated with chronic hemodialysis as beta-2 microglobulin. *Lab. Invest.,* 53:705, 1985.
7. Fenves, A.Z.; Emmett, M.; White, L.F.; Greenway, F.: Carpal tunnel syndrome with cystic bone lesions secondary to amyloidosis in chronic hemodialysis patients. *Am. J. Kidney Dis.,* 7:130, 1986.
8. Gorevic, P.D,.; Casey, T.T.; Stone, W.J.; et al.: Beta -2-microglobulin is an amylogenic protein in man. *J. Clin. Invest.,* 76:2425, 1985.
9. Munoz-Gomez, J.; Gomez-Perez, R.; Sole-Arques, M.; Llopart-Buisan, E.: Synovial fluid examination for the diagnosis of synovial amyloidosis in patients with chronic renal failure undergoing hemodialysis. *Ann. Rheum. Dis.,* 46:324, 1987.
10. Kuntz, D.; Naveau, B.; Bardin, T.; et al.: Destructive spondyloarthropathy in hemodialyzed patients: a new syndrome. *Arthritis Rheum.,* 27:369, 1984.
11. Schwarz, A.; Keller, F.; Seyfert, S.; Poll, W.; Molzahn, M; Distler, A.: Carpal tunnel syndrome: a major complication in long-term hemodialysis patients. *Clin. Nephol.,* 22:133, 1984.
12. Kenzora, J.E.: Dialysis carpal tunnel syndrome. *Orthopedics,* 1:195, 1978.
13. Jain, V.K.; Cestero, R.V.M.; Baum, J.: Carpal tunnel syndrome in patients undergoing maintenance hemodialysis. *JAMA,* 242:2868,1979.
14. Naito, M.; Ogata, K.; Goya, T.: Carpal tunnel syndrome in chronic renal dialysis patients: clinical evaluation of 62 hands and results of operative treatment. *J Hand Surg.,* 12B:366, 1986.
15. Kurer, M.H.J.; Baillod, R.A.; Madgwick, J.C.A.: Musculoskeletal manifestations of amyloidosis. *J. Bone Joint Surg.,* 73B, 2:271.
16. Asbury, A.K.; Victor, M.; Adams, R.D.: Uremic polyneuropathy. *Arch. Neurol.,* 8:413, 1963.
17. Bussel, J.A.; Abbot, J.A.; Lim, R.C.: A radial steal syndrome with AV fistula for hemodialysis. *Ann. Int. Med.,* 75:387, 1971.
18. Hampl, H.; Lobeck, H.; Bartil-Schwarze, S.; et al.: Clinical, morphologic, biochemical and immunohistochemical aspects of dialysis-associated amyloidosis. *Trans. Am. Soc. Artif. Intern. Organs.,* 33:250, 1987.
19. Laurent, G.; Calemard, E.; Charra, B.: Dialysis related amyloidosis. *Kidney. Int. Suppl.,* 24:532, 1988.
20. Teitz, C.C.; Delisa, J.A.; Halter, S.K.: Results of carpal tunnel release in renal hemodialysis patients. *Clin. Orthop. Rel. Res.,* 198:197, 1984.
21. Gilbert, M.S.; Robinson, A.; Baez, A.; et al.: Carpal tunnel syndrome in patients who are receiving long-term hemodialysis. *J. Bone Joint Surg.,* 70A:1145, 1988.
22. Drueke, T.B.: Beta-2-microglobulin amyloidosis and renal bone disease. *Miner. Elec. Metab.,* 17:261, 1991.
23. Flipo, R.M.; Le Loet, Siame, J.L. et al.: Destructive arthropathy of the hand in patients treated by long term hemodialysis. Seven cases with pathologic examination. *Rev. Rheum. (Engl. ED),* 62:241, 1995.
24. Gravallse, E.M.; Baker, N.; Lester, S. et al.: Musculoskeletal manifestations in β-2 microglobulin amyloidosis. *Arthritis Rheum.,* 35:592, 1992.
25. Ross, L.V.; Ross, G.J.; Mesgarzadeh, M.; et al.: Hemodialysis-related amyloidomas of bone. *Musculoskeletal Radiology,* 178:263, 1991.
26. Sargent, M.A.; Fleming, S.J.; Chattopadhyay, C.; et al.: Bone cysts and hemodialysis-related amyloidosis. *Clin. Radiol.,* 40:277, 1989.
27. DiRaimondo, C.R.; Casey, T.T.; DiRaimondo, C.V.; Stone, W.J.: Pathologic fractures associated with idiopathic amyloidosis of bone in hemodialysis patients. *Nephron.,* 43:22, 1986.
28. Ogawa, H.; Saito, A.; Hirabayashi, N.; Hara, K.: Amyloid deposition in systemic organs in long-term hemodialysis patients. *Clin. Nephrol.,* 28(4):199, 1987.